

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Risk of Bias

| Study | Random sequence generation | Allocation Concealment | Blinding (investigators) | Blinding (participants) | Selective Outcome Reporting | Missing Data | Overall bias |
|---------------------------------------|----------------------------|------------------------|--------------------------|-------------------------|-----------------------------|--------------|--------------|
| Bakim et al. ³¹ 2012 | 1 | 1 | 0.5 | 0.5 | 1 | 0.5 | unclear |
| Barbee et al. ³² 2011 | 1 | 1 | 1 | 1 | 1 | 1 | low |
| Bauer et al. ⁷⁵ 2018 | 1 | 1 | 1 | 1 | 1 | 0 | high |
| Bennabi et al. ⁷⁴ 2015 | 1 | 1 | 0.5 | 0.5 | 1 | 0.5 | unclear |
| Berman et al. ⁷³ 2007 | 1 | 1 | 1 | 1 | 1 | 1 | low |
| Berman et al. ³³ 2009 | 0.5 | 0.5 | 1 | 1 | 1 | 1 | unclear |
| Blumberger et al. ³⁵ 2012 | 1 | 1 | 1 | 1 | 1 | 0.5 | low |
| Blumberger et al. ³⁴ 2012 | 1 | 1 | 1 | 1 | 1 | 1 | low |
| Blumberger et al. ³⁶ 2016 | 1 | 1 | 1 | 1 | 1 | 1 | low |
| Boutros et al. ³⁷ 2002 | 1 | 1 | 1 | 1 | 1 | 0.5 | low |
| Chen et al. ³⁸ 2013 | 0.5 | 0.5 | 0.5 | 0.5 | 1 | 0.5 | high |
| Coenen et al. ⁷² 2019 | 0 | 0 | 1 | 1 | 1 | 1 | high |
| Concerto et al. ³⁹ 2015 | 0 | 0 | 0.5 | 1 | 1 | 1 | high |
| Dougherty et al. ⁴⁰ 2015 | 1 | 1 | 1 | 1 | 1 | 0.5 | low |
| Fava et al. ⁷⁷ 2015 | 0.5 | 0.5 | 0.5 | 0.5 | 1 | 0 | high |
| Fava et al. ⁴¹ 2018 | 1 | 1 | 1 | 1 | 1 | 1 | low |
| Fitzgerald et al. ⁴² 2012 | 0 | 0 | 1 | 1 | 1 | 0.5 | high |
| Garcia-Toro et al. ⁷⁶ 2001 | 0.5 | 0.5 | 1 | 1 | 0.5 | 1 | unclear |
| Garcia-Toro et al. ⁴³ 2006 | 0.5 | 0.5 | 1 | 1 | 0.5 | 1 | unclear |

| Study | Random sequence generation | Allocation Concealment | Blinding (investigators) | Blinding (participants) | Selective Outcome Reporting | Missing Data | Overall bias |
|---|----------------------------|------------------------|--------------------------|-------------------------|-----------------------------|--------------|--------------|
| Heresco-Levy et al. ⁴⁴ 2012 | 1 | 0.5 | 1 | 1 | 1 | 1 | low |
| Hobart et al. ⁴⁵ 2018 | 1 | 0.5 | 1 | 1 | 1 | 1 | low |
| Hobart et al. ⁷¹ 2018 | 0.5 | 1 | 1 | 1 | 1 | 0.5 | unclear |
| Holtzheimer et al. ⁴⁶ 2004 | 0.5 | 0 | 0.5 | 0.5 | 1 | 1 | unclear |
| Holtzheimer et al. ⁷⁰ 2017 | 1 | 1 | 1 | 1 | 1 | 1 | low |
| Husain et al. ⁶⁹ 2017 | 1 | 0.5 | 1 | 1 | 1 | 0.5 | unclear |
| Ionescu et al. ⁶⁸ 2019 | 1 | 0.5 | 1 | 1 | 1 | 1 | low |
| Kamijima et al. ⁶⁶ 2013 | 0.5 | 0.5 | 0.5 | 1 | 1 | 1 | unclear |
| Kamijima et al. ⁶⁷ 2018 | 0.5 | 1 | 1 | 1 | 1 | 1 | low |
| Kauffmann et al. ⁴⁷ 2004 | 0.5 | 0.5 | 1 | 0.5 | 1 | 1 | unclear |
| Li et al. ⁴⁸ 2014 | 0.5 | 0.5 | 1 | 0.5 | 1 | 1 | unclear |
| Marcus et al. ⁴⁹ 2008 | 0.5 | 0.5 | 0.5 | 1 | 1 | 0.5 | high |
| McAllister-Williams et al. ⁵⁰ 2015 | 1 | 1 | 1 | 1 | 1 | 0.5 | low |
| Mu-Hong Chen et al. ⁶⁵ 2019 | 0.5 | 0.5 | 0.5 | 0.5 | 1 | 0.5 | high |
| Nierenberg et al. ⁶⁴ 2003 | 0.5 | 0.5 | 0.5 | 1 | 1 | 1 | unclear |
| Palhano-Fontes et al. ⁶³ 2019 | 1 | 1 | 0.5 | 1 | 1 | 0.5 | unclear |
| Pallanti et al. ⁵¹ 2010 | 0.5 | 0.5 | 0.5 | 0.5 | 1 | 0.5 | high |
| Santos et al. ⁵² 2008 | 1 | 1 | 1 | 1 | 0 | 0.5 | high |
| Shelton et al. ⁵³ 2001 | 0.5 | 0.5 | 0.5 | 1 | 0.5 | 1 | high |
| Su et al. ⁶² 2017 | 0.5 | 0.5 | 0.5 | 1 | 1 | 1 | unclear |

| Study | Random sequence generation | Allocation Concealment | Blinding (investigators) | Blinding (participants) | Selective Outcome Reporting | Missing Data | Overall bias |
|---|----------------------------|------------------------|--------------------------|-------------------------|-----------------------------|--------------|--------------|
| Thase et al. ⁵⁴ 2015 | 1 | 0.5 | 0.5 | 1 | 0.5 | 0.5 | high |
| Thase et al. ⁵⁵ 2015 | 1 | 0.5 | 0.5 | 1 | 0.5 | 0.5 | high |
| Theleritis et al. ⁵⁶ 2017 | 1 | 1 | 0.5 | 0.5 | 1 | 0.5 | unclear |
| Theleritis et al. ⁵⁶ 2017 | 1 | 1 | 0.5 | 0.5 | 1 | 0.5 | unclear |
| Triggs et al. ⁵⁷ 2010 (left sham) | 0.5 | 0.5 | 1 | 1 | 1 | 1 | unclear |
| Triggs et al. ⁵⁷ 2010 (right sham) | 0.5 | 0.5 | 1 | 1 | 1 | 1 | unclear |
| Yesavage et al. ⁶¹ 2018 | 1 | 1 | 1 | 1 | 1 | 1 | low |
| Zheng et al. ⁶⁰ 2010 | 0.5 | 0 | 0.5 | 0.5 | 1 | 1 | high |
| Palm et al. ⁵⁹ 2012 | 1 | 1 | 0.5 | 1 | 1 | 1 | low |
| van Eijndhoven et al. ⁵⁸ 2020 | 0.5 | 0.5 | 0.5 | 0.5 | 1 | 0 | unclear |
| Rush et al. ⁷⁹ 2005 | 1 | 0.5 | 1 | 1 | 1 | 0 | high |
| Baeken et al. ⁸⁰ 2013 | 0 | 0.5 | 0 | 1 | 1 | 1 | high |
| Padberg et al. ⁷⁸ 1999 | 0.5 | 0.5 | 0.5 | 1 | 1 | 1 | unclear |

eTable 2. Subgroup analysis of treatment modalities

| Treatment Modality | B Coefficient and 95% CI | p value |
|----------------------------|--------------------------|---------|
| Pill | | Ref. |
| sham rTMS | -0.24 (-0.53 to 0.05) | 0.11 |
| Sham tDCS | 0.16 (-0.49 to 0.81) | 0.63 |
| Invasive brain stimulation | -0.21 (-0.64 to 0.22) | 0.33 |
| Parenteral | 0.21 (-0.36 to 0.78) | 0.47 |
| Liquid | -0.7 (-1.61 to 2.12) | 0.13 |

eTable 3. Clinical characteristics

| Author and year | Current Episode Length Mean (months)(SD) | Number of Past Episodes (mean) (SD) | Number of Trials Current Episode (mean) (SD) |
|--|--|-------------------------------------|--|
| Bakim et al. ³¹ 2012 | 17.7 (9.49) | 5 (2.6) | 3.3 (1.1) |
| Barbee et al. ³² 2011 | 31.8 (43.7) | 3.9 (4.6) | |
| Bauer et al. ⁷⁵ 2018 | 8.9 (13.2) | 3.4 (2.3) | |
| Bennabi et al. ⁷⁴ 2015 | NA | NA | NA |
| Berman et al. ⁷³ 2007 | 43.6 (53.8) | NA | 2.4 (0.6) |
| Berman et al. ³³ 2009 | 17.2 (NA) | 6.3 (10) | 2.3 (0.6) |
| Blumberger et al. ³⁵ 2012 | NA | 3.8 (3.7) | |
| Blumberger et al. ³⁴ 2012 | 40.8 (36) | 3.8 (3.7) | 4.1 (2.2) |
| Blumberger et al. ³⁶ 2016 | 46.9 (110.3) | 5.7 (6.7) | |
| Boutros et al. ³⁷ 2002 | | | |
| Chen et al. ³⁸ 2013 | | | |
| Coenen et al. ⁷² 2019 | 96 (84) | | 5.4 (4.9) |
| Concerto et al. ³⁹ 2015 | 17.2 (2.7) | 4.9 (0.9) | |
| Dougherty et al. ⁴⁰ 2015 | 141.6 (67.2) | 2.9 (2) | |
| Fava et al. ⁷⁷ 2015 | | | |
| Fava et al. ⁴¹ 2018 | 31.9 (62.1) | | |
| Fitzgerald et al. ⁴² 2012 | | 2.8 (2.8) | 4.9 (2.6) |
| Garcia-Toro et al. ⁷⁶ 2001 | | | |
| Garcia-Toro et al. ⁴³ 2006 | 32.6 (26.6) | 5.6 (4.4) | |
| Heresco-Levy et al. ⁴⁴ 2012 | 13.2 (14.3) | 3 (1.1) | |
| Hobart et al. ⁴⁵ 2018 | 11.7 (14.6) | 3.2 (2) | 2.2 (0.5) |
| Hobart et al. ⁷¹ 2018 | 19.4 (46.8) | 3.2 (2.4) | 2.2 (0.5) |
| Holtzheimer et al. ⁴⁶ 2004 | | | |
| Holtzheimer et al. ⁷⁰ 2017 | 116.0 (56.0) | 4.4 (3.6) | |
| Husain et al. ⁶⁹ 2017 | | | |
| Ionescu et al. ⁶⁸ 2019 | 91.6 (126.4) | 5.4 (5.2) | 8.2 (3.1) |
| Kamijima et al. ⁶⁶ 2013 | 15.6 (16.4) | | 2.5 (0.7) |
| Kamijima et al. ⁶⁷ 2018 | 15.8 (35.6) | | 2.4 (0.6) |
| Kauffmann et al. ⁴⁷ 2004 | | | |
| Li et al. ⁴⁸ 2014 | | | |
| Marcus et al. ⁴⁹ 2008 | 48.5 (88.8) | 7.3 (15.2) | 2.4 (0.6) |

Supplementary table 3. continued

| Author and year | Current Episode Length Mean (months)(SD) | Number of Past Episodes (mean) (SD) | Number of Trials Current Episode (mean) (SD) |
|---|--|-------------------------------------|--|
| Nierenberg et al. ⁶⁴ 2003 | 84.5 (94.9) | 0.9 (1.2) | 3.5 (2.6) |
| Palhano-Fontes et al. ⁶³ 2019 | 10.1 (9.15) | 3.5 (1.8) | 3.8 (1.9) |
| Pallanti et al. ⁵¹ 2010 | 9.44 (2.17) | 4.8 (2.7) | 6.0 (1.7) |
| Santos et al. ⁵² 2008 | 44.5 (66.1) | 6.9 (6.9) | |
| Shelton et al. ⁵³ 2001 | | | |
| Su et al. ⁶² 2017 | | | |
| Thase et al. ⁵⁴ 2015 | 13.7 (17.1) | 3.8 (2.9) | |
| Thase et al. ⁵⁵ 2015 | 16.9 (35) | 3.7 (4.9) | 2.24 0.467 |
| Theleritis et al. ⁵⁶ 2017 | | | |
| Theleritis et al. ⁵⁶ 2017 | | | |
| Triggs et al. ⁵⁷ 2010 (left sham) | | | |
| Triggs et al. ⁵⁷ 2010 (right sham) | . | | |
| Yesavage et al. ⁶¹ 2018 | | | |
| Zheng et al. ⁶⁰ 2010 | 54 (32.4) | | |
| Palm et al. ⁵⁹ 2012 | 9 (15) | | |
| van Eijndhoven et al. ⁵⁸ 2020 | 57.9 (54.8) | 3.5 (1.3) | |
| Rush et al. ⁷⁹ 2005 | 51.7 (52.2) | | 3.4 (1.7) |
| Baeken et al. ⁸⁰ 2013 | 5.3 (4.5) | | |
| Padberg et al. ⁷⁸ 1999 | 48 (48) | | |

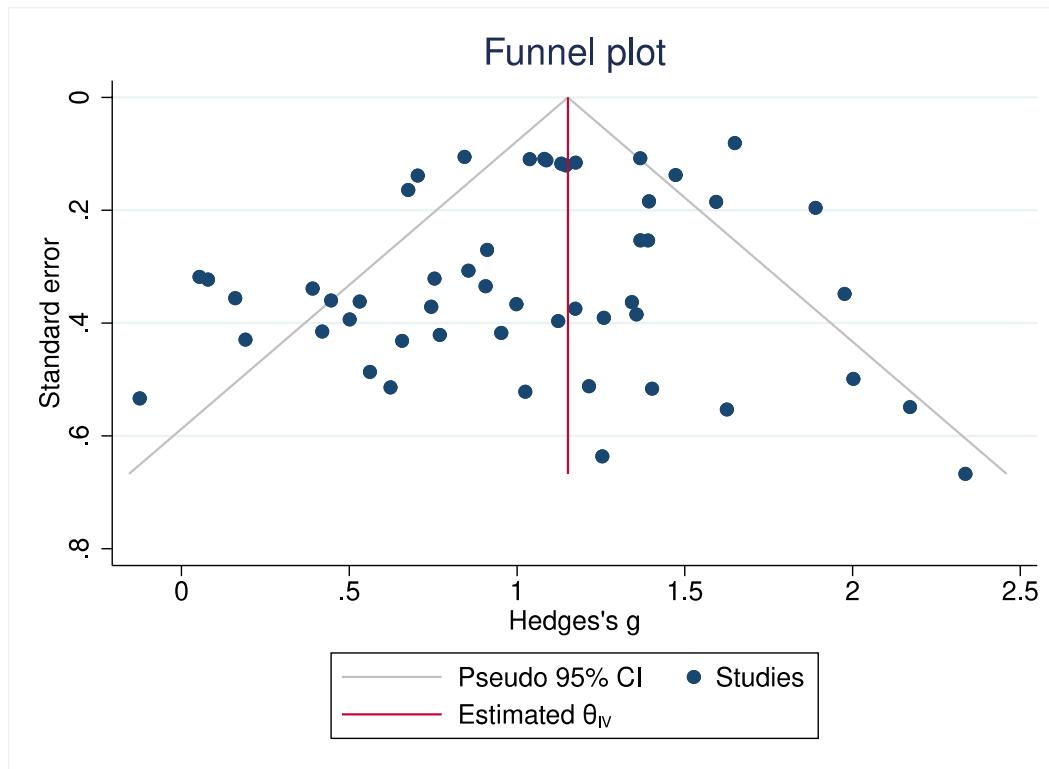
eAppendix 1. Components of the Randomized Effect model used for our analyses

The full statistic description of the Random-effect model and meta-analysis estimation methods used in Stata 17 can be found online on: <https://www.stata.com/manuals/meta.pdf>

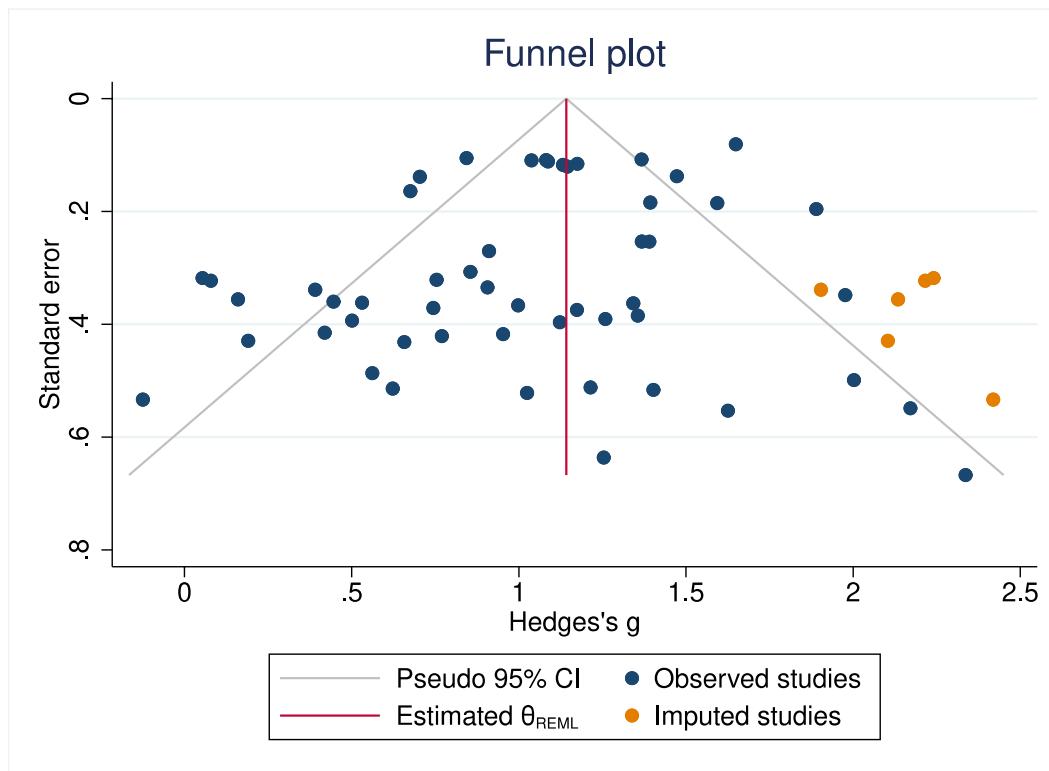
eAppendix 2. Search Strategy:

Searches were conducted on MEDLINE Web of Science and PsychInfo from inception to January 24th 2020. Key terms, notable papers, and citation lists were reviewed for additional studies. Search terms used were (depress* OR MDD OR major depress*) AND (resistan* OR refractor* OR non-respon* OR nonrespon* OR un-respon* OR unrespon* OR TRD OR fail* OR inadequate OR difficult OR intractable) AND (placebo OR sham OR control OR controlled) AND (randomi* OR RCT) AND (treatment OR intervention OR trial).

eFigure 1. Funnel plot of included studies



eFigure 2. Trim and fill funnel plot



eFigure 3. Forest plot of main placebo effect size Grouped by risk of bias

| Study | Baseline | | | Endpoint | | | Hedges's g with 95% CI | Weight (%) |
|---|----------|-------|------|----------|-------|-------|------------------------|------------|
| | N | Mean | SD | N | Mean | SD | | |
| Low | | | | | | | | |
| Barbee et al. 2011 | 48 | 26.63 | 4.88 | 31 | 17.37 | 8.62 | -0.99 [-1.89, -0.99] | 2.24 |
| Berman et al. 2007 | 176 | 25.9 | 6.5 | 160 | 20.1 | 2.9 | -0.99 [0.90, 1.36] | 3.01 |
| Blumberger et al. 2012 | 11 | 24.1 | 2.9 | 7 | 18.1 | 5.5 | -0.99 [0.39, 2.41] | 1.11 |
| Blumberger et al. 2012 | 22 | 25.2 | 2.8 | 15 | 18.9 | 6.4 | -0.99 [0.63, 2.05] | 1.68 |
| Blumberger et al. 2016 | 41 | 25.5 | 3.6 | 35 | 20.5 | 3.64 | -0.99 [0.87, 1.96] | 2.25 |
| Boutros et al. 2002 | 9 | 31.7 | 4.9 | 7 | 25.4 | 12.4 | -0.99 [-0.39, 1.52] | 1.20 |
| Dougherty et al. 2015 | 14 | 36.4 | 3.3 | 14 | 27.4 | 10.5 | -0.99 [0.35, 1.90] | 1.53 |
| Fava et al. 2018 | 81 | 26.4 | 6.3 | 72 | 18.4 | 2.89 | -0.99 [-0.23, 1.96] | 2.64 |
| Heresco-Levy et al. 2012 | 13 | 27.2 | 4.9 | 12 | 23.3 | 9.6 | -0.99 [-0.27, 1.27] | 1.54 |
| Hobart et al. 2018 | 202 | 26.2 | 6.2 | 96 | 18.1 | 3.53 | -0.99 [1.20, 1.74] | 2.91 |
| Holtzheimer et al. 2017 | 30 | 37.3 | 3.8 | 29 | 30 | 10.6 | -0.99 [0.38, 1.44] | 2.15 |
| Ionescu et al. 2019 | 13 | 26.3 | 4.8 | 10 | 20 | 10.7 | -0.99 [-0.06, 1.59] | 1.43 |
| Kamijima et al. 2018 | 203 | 25.2 | 6.5 | 183 | 18 | 6.8 | -0.99 [0.87, 1.30] | 3.05 |
| McAllister-Williams et al. 2015 | 82 | 28.1 | 5.4 | 74 | 22.6 | 10.3 | -0.99 [0.35, 1.00] | 2.76 |
| Palm et al. 2012 | 11 | 34.6 | 5.4 | 10 | 30.2 | 7.4 | -0.99 [-0.19, 1.50] | 1.39 |
| Yesavage et al. 2018 | 83 | 27.5 | 5.1 | 68 | 14.4 | 8.6 | -0.99 [1.51, 2.27] | 2.58 |
| Heterogeneity: $\tau^2 = 0.09$, $I^2 = 67.67\%$, $H^2 = 3.09$ | | | | | | | | |
| Test of $0 = 0$; $Q(15) = 42.58$, $p < 0.001$ | | | | | | | | |
| Unclear | | | | | | | | |
| Bakiri et al. 2012 | 12 | 25.58 | 3.82 | 12 | 19.5 | 7.83 | -0.99 [0.13, 1.77] | 1.45 |
| Bennabi et al. 2015 | 12 | 24.2 | 5.6 | 11 | 13.17 | 4.97 | -0.99 [1.02, 2.98] | 1.17 |
| Berman et al. 2009 | 172 | 27.1 | 5.8 | 149 | 20.7 | 5.3 | -0.99 [0.91, 1.38] | 2.99 |
| Garcia-Torres et al. 2001 | 18 | 25.6 | 4.92 | 16 | 23.83 | 3.78 | -0.99 [-0.27, 1.05] | 1.79 |
| Garcia-Torres et al. 2006 | 10 | 25.1 | 7.28 | 10 | 23.6 | 7.79 | -0.99 [-0.65, 1.03] | 1.40 |
| Hobart et al. 2018 2 | 208 | 25.4 | 5.2 | 186 | 20.8 | 5.7 | -0.99 [0.64, 1.05] | 3.06 |
| Holtzheimer et al. 2004 | 8 | 20.8 | 6.3 | 7 | 15.3 | 3 | -0.99 [0.00, 2.05] | 1.10 |
| Husain et al. 2017 | 20 | 32.6 | 10.1 | 18 | 32 | 11.8 | -0.99 [-0.57, 0.68] | 1.89 |
| Kamijima et al. 2013 | 195 | 25.5 | 7.4 | 183 | 18.1 | 6.8 | -0.99 [0.82, 1.25] | 3.04 |
| Kaufmann et al. 2004 | 5 | 18.2 | 4.9 | 5 | 11.8 | 4.3 | -0.99 [0.01, 2.50] | 0.83 |
| Li et al. 2014 | 15 | 23.8 | 3.2 | 15 | 19.66 | 3.2 | -0.99 [0.49, 2.02] | 1.56 |
| Nieremberg et al. 2003 | 17 | 21.7 | 4.2 | 15 | 15.1 | 5.3 | -0.99 [0.60, 2.11] | 1.58 |
| Padberg et al. 1999 | 6 | 22.2 | 8.4 | 6 | 23.5 | 10.4 | -0.99 [-1.17, 0.92] | 1.07 |
| Palharo-Fontes et al. 2019 | 15 | 19.73 | 4.59 | 15 | 16.92 | 7.36 | -0.99 [0.45, 0.26] | 1.15 |
| Su et al. 2017 | 24 | 23.3 | 4.1 | 24 | 13.78 | 5.3 | -0.99 [1.29, 2.66] | 1.75 |
| Thelektis et al. 2017 | 20 | 29.4 | 3.2 | 18 | 25.4 | 5.3 | -0.99 [0.25, 1.56] | 1.81 |
| Thelektis et al. 2017 2 | 24 | 30.3 | 3.6 | 21 | 27 | 4 | -0.99 [0.25, 1.46] | 1.95 |
| Triggs et al. 2010 (left sham) | 7 | 27.7 | 3.5 | 7 | 22 | 11.6 | -0.99 [0.62, 1.38] | 1.12 |
| Triggs et al. 2010 (right sham) | 7 | 27.3 | 2.7 | 7 | 13.4 | 7.4 | -0.99 [0.24, 0.36] | 0.77 |
| Heterogeneity: $\tau^2 = 0.16$, $I^2 = 71.12\%$, $H^2 = 3.46$ | | | | | | | | |
| Test of $0 = 0$; $Q(18) = 44.00$, $p < 0.001$ | | | | | | | | |
| High | | | | | | | | |
| Baeken et al. 2013 | 11 | 26.45 | 8.71 | 11 | 22.36 | 10.01 | -0.99 [-0.39, 1.23] | 1.46 |
| Bauer et al. 2018 | 441 | 25.8 | 4.1 | 381 | 12.41 | 11.07 | -0.99 [1.65, 1.49] | 3.16 |
| Chen et al. 2013 | 10 | 24.9 | 6.3 | 10 | 12.3 | 4.7 | -0.99 [2.17, 1.10] | 3.05 |
| Coenen et al. 2019 | 8 | 29.6 | 4 | 8 | 21.46 | 5.37 | -0.99 [1.63, 0.54] | 2.71 |
| Concerto et al. 2015 | 15 | 21 | 5 | 15 | 20 | 7 | -0.99 [0.16, 0.86] | 1.71 |
| Fava et al. 2015 | 85 | 29.1 | 5.5 | 63 | 20.8 | 6.46 | -0.99 [1.39, 1.03] | 2.65 |
| Fitzgerald et al. 2012 | 20 | 22.9 | 2.1 | 17 | 22.6 | 5 | -0.99 [0.08, 0.55] | 1.87 |
| Marcus et al. 2008 | 190 | 27 | 5.5 | 162 | 21.3 | 3.33 | -0.99 [1.17, 0.95] | 3.02 |
| Mu-Hong Chen et al. 2019 | 16 | 34 | 4.7 | 16 | 26.1 | 8 | -0.99 [1.17, 0.44] | 1.63 |
| Pallanti et al. 2010 | 20 | 29.05 | 3.94 | 20 | 26.38 | 3.4 | -0.99 [0.75, 0.12] | 1.88 |
| Rush et al. 2005 | 110 | 29.7 | 5.2 | 110 | 25.1 | 7.6 | -0.99 [0.70, 0.43] | 2.90 |
| Santos et al. 2006 | 17 | 28.4 | 7.7 | 13 | 21.2 | 11.3 | -0.99 [0.74, 0.02] | 1.64 |
| Shelton et al. 2001 | 10 | 27.7 | 4.2 | 7 | 20.8 | 6.8 | -0.99 [1.21, 0.21] | 1.13 |
| Thase et al. 2015 1 | 191 | 27.1 | 5.6 | 179 | 21.95 | 3.56 | -0.99 [1.09, 0.87] | 3.01 |
| Thase et al. 2015 2 | 221 | 26.3 | 5.3 | 203 | 20 | 3.69 | -0.99 [1.37, 1.16] | 3.05 |
| Zheng et al. 2010 | 15 | 24.6 | 2.8 | 15 | 22.9 | 3.4 | -0.99 [0.53, 0.18] | 1.68 |
| van Eijndhoven et al. 2020 | 16 | 22.7 | 3.8 | 16 | 18.6 | 4.2 | -0.99 [1.00, 0.28] | 1.66 |
| Heterogeneity: $\tau^2 = 0.16$, $I^2 = 82.32\%$, $H^2 = 5.66$ | | | | | | | | |
| Test of $0 = 0$; $Q(16) = 82.63$, $p < 0.001$ | | | | | | | | |
| Overall | | | | | | | | |
| Heterogeneity: $\tau^2 = 0.14$, $I^2 = 76.19\%$, $H^2 = 4.20$ | | | | | | | | |
| Test of $0 = 0$; $Q(51) = 165.86$, $p < 0.001$ | | | | | | | | |
| Test of group differences: $Q_2(2) = 2.34$, $p = 0.31$ | | | | | | | | |

Random-effects REML model